

## Cardiovascular risk after orthotopic liver transplantation, a review of the literature and preliminary results of a prospective study

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### Abstract

Improved surgical techniques and greater efficacy of new anti-rejection drugs have significantly improved the survival of patients undergoing orthotopic liver transplantation (OLT). This has led to an increased incidence of metabolic disorders as well as cardiovascular and cerebrovascular diseases as causes of morbidity and mortality in OLT patients. In the last decade, several studies have examined which predisposing factors lead to increased cardiovascular risk (*i.e.*, age, ethnicity, diabetes, NASH, atrial fibrillation, and some echocardiographic parameters) as well as which factors after OLT (*i.e.*, weight gain, metabolic syndrome, immunosuppressive therapy, and renal failure) are linked to increased cardiovascular mortality. However, currently, there are no available data that evaluate the development of atherosclerotic damage after OLT. The awareness of high cardiovascular risk after OLT has not only lead to the definition of new but generally not accepted screening of high risk patients before transplantation, but also to the need for careful patient follow up and treatment to control metabolic and cardiovascular pathologies after transplant. Prospective studies are needed to better define the predisposing factors for recurrence and *de novo* occurrence of metabolic alterations responsible for cardiovascular damage after OLT. Moreover, such studies will help to identify the timing of disease progression and damage,

which in turn may help to prevent morbidity and mortality for cardiovascular diseases. Our preliminary results show early occurrence of atherosclerotic damage, which is already present a few weeks following OLT, suggesting that specific, patient-tailored therapies should be started immediately post OLT.

**Key words:** Orthotopic liver transplant; Cardiovascular risk; Atherosclerosis, Non-alcoholic fatty liver disease; Intima-media thickness; Epicardial fat thickness; Diastolic dysfunction

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**Core tip:** Due to better immunosuppressive therapies, the survival of liver transplantation recipients is improved, but an increased incidence of metabolic disorders as well as cardiovascular and cerebrovascular diseases as causes of morbidity and mortality is observed. This review analyzes risk factors [before orthotopic liver transplantation (OLT) and occurring *de novo* after OLT] leading to cardiovascular diseases and the current tools to identify high risk patients. We also provide preliminary data from one of the first prospective studies on the evolution of cardiovascular damage in adult patients submitted to OLT.

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## EVIDENCE OF CARDIOVASCULAR DISEASE IN PATIENTS SUBMITTED TO ORTHOTOPIC LIVER TRANSPLANTATION

Orthotopic liver transplantation (OLT) represents the only therapy for several end stage liver diseases of different etiology. In Europe as well as in United States nearly 6000 patients/year are submitted to liver transplantation<sup>[1,2]</sup>.

According to the United Network for Organ Sharing registry, the survival rate at 1, 5 and 10 years after OLT is respectively of 85%, 70% and 50%<sup>[2]</sup>. Similarly, according to the European Liver Transplant Registry<sup>[1]</sup>, the survival rate at 1, 5, 10, 15, 20 years after OLT is of 82%, 71%, 61%, 51% and 43%. However, various diseases have emerged as possible causes of post OLT complications. During the first 6 mo post-transplant, the highest risk of death was observed (11% mortality rate), while between 6 mo and 8 years post OLT, it rated at 2.5%-5%. Such mortality value increased again after 8 years to 6%-7%.

In a recent study including 798 transplanted

subjects followed for a median of 10 years<sup>[3]</sup>, in which 327 deaths were reported, malignancy was the first cause of death followed by cardiovascular causes, infective diseases and renal failure, accounting for 22%, 11%, 9% and 6% of death, respectively.

As cardiovascular diseases emerged as a leading cause of death, several studies have been proposed in order to understand the predisposing factors leading to cardiovascular disease, as well as the post-OLT conditions facilitating cardiovascular morbidity (*de novo* diseases). However, scanty data are available in prospective studies.

## RISK FACTORS OF CARDIOVASCULAR COMPLICATIONS AFTER OLT

Pre-existing cardio-metabolic pathologies and *de novo* occurrence, partly associated with immunosuppressive therapy, are considered the main causes of post-transplant cardiovascular complications<sup>[4]</sup>.

### *Pre-existing metabolic factors/non-alcoholic fatty liver disease*

The relevance of cardiometabolic pathologies reflects the ongoing epidemic of obesity and diabetes in the United States<sup>[5,6]</sup> and all over the Western countries. This is further documented by the marked increase in the prevalence of diabetes among candidates to OLT independently of etiology. Another metabolic disease recently recognized to have a strong role in OLT is non-alcoholic fatty liver disease (NAFLD), considered a manifestation of the metabolic syndrome (MS) or even suggested to precede MS, of which insulin resistance is the hallmark. NAFLD is the most frequent cause of liver disease in Western countries and is likely to become the most common indication for OLT over the next decade<sup>[7,8]</sup>.

Non-alcoholic steatohepatitis (NASH) represents 20%-25% of all NAFLD and may potentially evolve to cirrhosis and hepatocellular carcinoma, besides carrying all cardiovascular risks typically associated to MS<sup>[9]</sup>. Interestingly, Targher *et al.*<sup>[10]</sup> reported that NASH-affected patients are at increased risk of atrial fibrillation, which was recently identified as a severe risk factor for OLT<sup>[11]</sup>. In an analysis performed by Van Wagner *et al.*<sup>[12]</sup>, atrial fibrillation was one of the factors independently associated with major adverse cardiovascular events, especially in patients with a previous history of NASH and alcoholic cirrhosis. Indeed, a positive history of atrial fibrillation before liver transplantation was significantly more frequent in patients with major adverse cardiovascular events than in those without a previous episode of atrial fibrillation<sup>[13]</sup>.

Several studies pointed out the relationship between NAFLD and cardiovascular mortality in patients submitted to OLT. Overweight/obesity, dyslipidemia, hypertension and glucose metabolism abnormalities

are typical alterations detected with a high frequency in patients with NAFLD and they also define MS., notably, they have all been associated with high morbidity and mortality in patients submitted to OLT<sup>[14,15]</sup>. In addition, patients with NAFLD have been reported to be at risk for chronic kidney disease, which is another known risk factor for CVD<sup>[16,17]</sup>. The strong association between NAFLD and chronic kidney disease suggests that NAFLD could be used to stratify patients undergoing liver or kidney transplantation for a better evaluation of CV risk<sup>[18]</sup>.

In line with the importance of NAFLD in the history of patients undergoing OLT, Laish *et al.*<sup>[19]</sup> found in a retrospective analysis that pretransplant NAFLD, body mass index, diabetes, and triglycerides levels were predisposing factors for the recurrence of post-transplant MS and that post-transplant MS was associated with cardiovascular morbidity and mortality.

Alteration of glucose metabolism, one of the major complications of NAFLD/MS, is already recognized to be associated with a worse prognosis (increased risk of cirrhosis and hepatocellular carcinoma occurrence) in patients with chronic liver disease, independently from the etiology (HCV chronic hepatitis, NAFLD). In particular, its presence is also associated with a worse clinical history of transplanted patients. Several studies performed in large cohorts of transplanted patients reported that both patients and graft survival was negatively associated with pre-existing diabetes or with *de novo* occurrence of diabetes after OLT<sup>[20,21]</sup>.

In addition, it has been reported that subjects with type 1 diabetes had a significantly lower survival than subjects with type 2 diabetes and, in turn the latter had a reduced survival compared to patients without diabetes<sup>[20]</sup>.

The role of diabetes and NAFLD in the natural history of OLT is further demonstrated by the evidence that patients undergoing OLT for NASH related cirrhosis showed significantly higher risk of CVD, either in the first 30 d<sup>[22]</sup> or within 3 years post OLT, compared with patients undergoing transplantation for other chronic liver diseases such as primary biliary and sclerosing cholangitis<sup>[23]</sup>. However, overall survival did not differ. In addition, a strong association between adverse CVD events and post-transplant hypertension and diabetes was observed, with a double risk of CVD if both comorbidities coexisted. However, conflicting data were recently obtained in a large prospective study performed in United Kingdom, including almost 4000 subjects recipients of liver transplant, with diabetes having no impact on mortality at any time after OLT<sup>[24-29]</sup>. The Authors have speculated that the intensive screenings for cardiovascular complications in the diabetic liver transplant candidates of the cohort studied could explain these unexpected results. Thus, they emphasize the importance of a careful screening and selection of the candidates to OLT, of their follow up as well as of an active diabetes management after transplantation. Such procedures could lead recipients

with diabetes to have outcomes comparable to those of recipients without diabetes.

Although malnutrition is commonly observed in patients with end stage liver disease, obesity is a metabolic problem that impacts negatively both on immediate and long-term survival. Most patients in the United States who underwent liver transplantations between 1988 and 1996 were overweight, reflecting the epidemic of obesity. Obesity was more common in women and in patients with cryptogenic cirrhosis, suggesting that the so called cryptogenic cirrhosis was in truth a metabolic cirrhosis. Severe obesity (BMI > 40 kg/m<sup>2</sup>) was associated with decreased 30-d, 1-year, and 2-year survival, while five-year survival was reduced even in patients with BMI > 35 kg/m<sup>2</sup><sup>[30]</sup>.

## DE NOVO OCCURRENCE OF METABOLIC ALTERATIONS AFTER OLT

It is very well known that recurrence or *de novo* occurrence of NAFLD post OLT as well as after kidney transplantation may facilitate MS happening<sup>[21,31-37]</sup>. However it is difficult to define the prevalence of MS after OLT due to malnutrition, which is usually present in most cirrhotic candidates to OLT, and which ameliorates after transplantation. This is followed, in the first years after OLT, by a marked increase in body weight, which in almost 20% of cases reaches the level of obesity with an increase of BMI of 60%-70% compared to the pretransplant one. The increase in weight is almost always associated with the development of NAFLD, which in turn is accompanied by insulin resistance, the hallmark of MS and of NAFLD, present in 20%-58% of cases, glucose intolerance/diabetes, altered lipids metabolism in 50%-70%, and very often hypertension in 60%-70%<sup>[21,36,38-41]</sup>. Altogether, this also contributes to the induction of systemic and renal vasoconstriction, as well as impaired sodium excretion when treated with immunosuppressive drugs.

Interestingly, obesity in liver donors is also a predictor of liver steatosis in the liver recipients, and the presence of steatosis in the donor liver is strongly related to decreased allograft function and patient survival, with a high probability of NASH development. This has led to the decision that grafts with steatosis greater than 60% cannot be used for liver transplant<sup>[22]</sup>.

New-onset diabetes mellitus, a well described complication following solid organ transplantation (liver, lung and kidney), occurs in 2% to 53% of all solid organ transplants, in 4% to 25% of renal transplant recipients and in 2.5% to 25% of liver-transplants<sup>[42-48]</sup> and is associated with an increased risk of cardiovascular morbidity and infection, as well as reduced quality of life, impaired graft function and lower patient survival<sup>[21,43,48,49]</sup>. *De novo* diabetes after OLT has been associated with hepatitis C virus

**Table 1** Incidence or prevalence of risk factors of the different manifestations of the metabolic syndrome after orthotopic liver transplantation

Disease	Incidence/prevalence	Risk factors	Ref.
Diabetes mellitus	9%-21% (incidence)	Male gender High pre-LT BMI Family history Hepatitis C Older age immunosuppressants rapamycin gene polymorphisms TCF7L2 gene polymorphisms (donor)	[65,105-107]
Hyperlipidemia	45%-69% (prevalence)	Diet Older age High BMI DM Renal impairment, immunosuppressants low-density lipoprotein receptor gene polymorphism (donor)	[38,108-110]
Arterial hypertension	60%-70% (prevalence)	Obesity Older age Impaired glycemia Immunosuppressants	[106,111,112]
Overweight-obesity	24%-31% (prevalence)	High BMI before LT Diet Immunosuppressants	[113-116]
Metabolic syndrome	40%-60% (prevalence)	Older age Obesity and increased BMI pre-LT DM Genetic polymorphisms in the living donor High-dosage immunosuppressive drugs Changes in intestinal microbiota DM	[33,106,117,118]
NAFLD/NASH	18%-100% (incidence of NAFLD in NASH and cryptogenic recipients) 0%-14% (incidence of NASH in NASH and cryptogenic recipients) 10%-40% (incidence of NAFLD in non-NASH or cryptogenic recipients)	Obesity and weight gain, dyslipidemia Genetic predisposition (presence of the rs738409-G allele of the Patatin-like phospholipase) Arterial hypertension Immunosuppressant pre-LT alcoholic cirrhosis Liver graft steatosis	[18,33,80,119-124]

NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis.

infection, pre-existing NAFLD, increased BMI, use of tacrolimus (as opposed to ciclosporine), steroids, age, and ethnicity<sup>[43,44,50-52]</sup>. In kidney transplant recipients variables predictors of new onset diabetes were similar to those of OLT, being crucial the early detection and management. Table 1 lists risk factors leading to metabolic syndrome and its different clinical manifestations after OLT.

## IMMUNOSUPPRESSIVE THERAPY AND METABOLIC ALTERATIONS

The use of highly effective anti-rejection medications has led to improved survival, albeit with evidence of well-recognized side effects such as metabolic derangements, and an overall increase in MS and insulin resistance after OLT.

Steroids decrease insulin production by beta-cells, increase gluconeogenesis and reduce glucose utilization, thus strongly contributing to the occurrence of diabetes and weight gain. Tacrolimus and cyclosporine A, the calcineurin inhibitors (CNIs),

facilitate *de novo* occurrence of diabetes by decreasing insulin production and inducing insulin resistance, which is followed by hyperinsulinemia, the effect being more severe for tacrolimus. In addition to these effects increased oxidative stress and lipid peroxidation also occur, followed by hypertension, dyslipidemia and kidney damage<sup>[36,53-64]</sup>.

Among other immunosuppressive drugs demonstrated to exert negative cardiovascular effects is sirolimus, which was reported to be complicated by serious adverse events including hepatic artery thrombosis and wound healing complications within the first 30 d after OLT<sup>[65]</sup>. Thus, sirolimus was not approved in liver transplantation, although recent studies using lower doses showed an improved safety profile<sup>[66,67]</sup>. Viceversa, everolimus provides a new therapeutic option for liver transplant recipients, when introduced early after liver transplantation<sup>[68]</sup> particularly with respect to posttransplant nephrotoxicity and other adverse events associated with long-term administration of CNIs.

Several studies<sup>[69-71]</sup> showed that hyperlipidemia was more frequent in the everolimus-treated patients

**Table 2** Most used immunosuppressive drugs and main metabolic side effects

Factor	Metabolic consequences	Ref.
Steroid	Increased fat deposition with truncal fat distribution	[36,53-55]
	Decreased fat oxidation	
	Increased gluconeogenesis	
	Obesity	
	Decreased glucose utilization	
	Decreased b-cell insulin production	
	Increased proteolysis,	
	Reduced protein synthesis	
	Insulin resistance	
	Diabetes, NAFLD	
	Mineralocorticoids effects	
	Sodium retention	
	Hypertension	
	Hyperlipemia	
	Tacrolimus:	
Calcineurin inhibitor	b-cell toxicity	[58-65]
	Decreased insulin secretion	
	Insulin resistance,	
	Diabetes (more than cyclosporine)	
	Cyclosporine:	
	Decreased energy metabolism and muscle mass obesity	
	Weight gain	
	Decreased cholesterol transport into bile hyperlipidemia	
	Occupy LDL receptor	
	(more than tacrolimus)	
	Renal vasoconstriction	
	Hypertension	
	(more than tacrolimus)	
	Increase insulin response	
	Block b-cell proliferation	
mTOR inhibitor	Alter insulin signaling	[68,125-129]
	Decreased diabetes	
	Increased diabetes	
	Increased triglyceride production pathways	
	And secretion	
	Increased adipose tissue lipase activity	
	Hyperlipidemia	
	Decreased Lipoprotein lipase activity	
	Mycophenolate mofetil:	
	No nephrotoxicity	
	No effect on lipid profile, hypertension or diabetes mellitus	
	Azathioprine:	
	Vascular calcification	
	Arteriosclerosis	
	Basiliximab	
Anti-metabolites	No nephrotoxicity	[145-149]
	Rare effect on lipid profile, hypertension and diabetes mellitus	
Monoclonal antibodies		[150]

than in those treated with CNIs. The relationship between dyslipidemia during mTOR inhibitor administration and cardiovascular outcomes has not been systematically evaluated, and thus the clinical effect of these adverse events is not fully understood. However, the proportion of patients receiving lipid lowering treatment was similar when everolimus associated to a reduced doses of tacrolimus or the standard-of-care tacrolimus treatment were given<sup>[72]</sup>. Furthermore, the incidence of cardiovascular events after 24 mo did not differ between the two treatment groups<sup>[70]</sup>. The relationship between high rates of dyslipidemia and mTOR inhibitor use (sirolimus and everolimus), either in conjunction with or instead of CNIs, may be due to altered insulin signaling pathways that result in excess

triglyceride production and secretion.

Thus, it is evident that the type of immunosuppressive therapy may strongly influence the occurrence of metabolic complications (Table 2).

### **NAFLD, A LEADING CAUSE OF OLT, ALSO COMPLICATES OLT DUE TO ITS FREQUENT RECURRENCE OR *DE NOVO* OCCURRENCE**

In the last 10 years a marked increase of OLT for NASH cirrhosis was observed while that of HCV remained stable<sup>[36]</sup>. Thus NAFLD is expected to become the most



common indication for OLT over the next decade, given that HCV related morbidity will progressively decrease. Post-transplant NAFLD can be due to the recurrence of pretransplant MS and NAFLD, but often develops *de novo* because of modified metabolic conditions and use of the immunosuppressive drugs. NAFLD recurrence post-liver transplantation may progress to end-stage disease with liver failure and a need for retransplantation<sup>[73-76]</sup>. NAFLD incidence after liver transplantation ranges from 18 to 40% and that of NASH between 9%-13%. In addition, in patients transplanted for cryptogenic cirrhosis, the time-dependent risk of developing allograft steatosis is 100% over 5 years<sup>[40,75,77,78]</sup>, indirectly confirming that cryptogenic cirrhosis is an evolution of NASH.

It is also worth noting that genetic background seems to play a role in allograft steatosis, since post-transplant NAFLD risk is linked to a polymorphism in adiponectin (PNPLA3), which mediates triglyceride hydrolysis and has been reported to be the strongest genetic factor for liver steatosis, independently of insulin resistance. This polymorphism has been repeatedly reported to be associated with more severe fibrosis in patients with NASH and is also associated with pre-transplant obesity risk and presence of steatosis in the donor graft<sup>[79,80]</sup>.

The natural history of post-transplant *de novo* NAFLD is poorly understood, but it may contribute to increased CVD mortality, since NAFLD is an independent risk factor for CVD even in non-cirrhotic patients<sup>[34,77,81]</sup>.

It is very likely that the mediator of these processes is insulin resistance, which is linked to weight gain and high-dose steroid use post-transplantation, and is reflected by worsening of glucose tolerance, and underlies all manifestations of MS<sup>[76,81,82]</sup>. Overall, the main consequences of post-transplant MS appear to be NAFLD recurrence/development, higher incidence of adverse CVD events, and chronic transplant nephropathy<sup>[64]</sup>.

Taken together, these evidence clearly demonstrate that a strict selection of patients with a complete cardiovascular assessment is necessary before listing patients for OLT in order to optimize resources and start early therapy to prevent complications.

## CARDIOVASCULAR SCREENING PRE-OLT

In patients with cirrhosis, a clinical syndrome named cirrhotic cardiomyopathy has been noticed. This pathology is defined as a blunted contractile responsiveness to physiologic, pathologic, or pharmacologic stress and/or altered diastolic relaxation with electrophysiological abnormalities but with normal increased cardiac output and contractility at rest, in the absence of known cardiac disease and irrespective of the causes of cirrhosis<sup>[83]</sup>. Strict diagnostic criteria are

lacking and this syndrome often goes unrecognized.

Van Wagner, as previously reported, showed that non coronary incidents represent the major adverse cardiovascular events after OLT, including atrial fibrillation, heart failure, thromboembolism and stroke<sup>[11]</sup>.

This suggests that some OLT candidates may have subclinical CVD and may not be identified as patients at high risk when using standard risk algorithms. A study designed to evaluate the association between the presence of segmental myocardial perfusion defects pre-OLT by using myocardial perfusion scintigraphy and the occurrence of post-OLT complications and 1-year mortality after OLT, showed that even the presence of a single reversible perfusion defect was significantly related to an increased incidence of 1-year all-cause mortality. Due to these results the authors suggest the use of myocardial perfusion scintigraphy in the work up process<sup>[84]</sup>. Other studies point out the attention to pre-transplant pathology detected by echocardiography, including valve regurgitation, pulmonary artery pressure, right and left ventricular size, systolic function and left ventricular ejection fraction<sup>[85-87]</sup>. One study found a positive association between left ventricular hypertrophy and post-transplant death<sup>[85]</sup>, whereas others yielded conflicting results regarding tricuspid regurgitation and post-transplant death<sup>[86,87]</sup>.

Bushyhead *et al.*<sup>[88]</sup> tried to determine if specific findings in pre-transplant echocardiography were associated with post-transplant survival and the development of cardiovascular and renal disease. The results of this study showed that increasing pulmonary artery systolic pressure was associated with significantly increased risk of hospitalization for myocardial infarction or heart failure, while increased left ventricular ejection fraction, a possible expression of cirrhotic cardiomyopathy, was associated with a non-significant increased risk of stage 4 or 5 chronic kidney disease.

Thus, because of the high risk of cardiovascular complications after OLT, careful preoperative evaluation of coronary risk is assessed in every transplant center. However, there is not yet a general agreement on a standard cardiovascular screening in OLT candidates. European guidelines suggest that electrocardiogram and echocardiography should be performed in all liver transplant candidates. If the patient has multiple cardiovascular risk factors, and is older than 50 years, a more extensive work up has to be assessed, including a cardiopulmonary exercise test to uncover asymptomatic ischaemic heart disease<sup>[89]</sup>. If the target heart rate is not achieved during a standard exercise test, a pharmacological stress test is the test of choice. If coronary disease is suspected, coronary angiography should be performed<sup>[90]</sup>.

## THERAPY AND FOLLOW UP AFTER LIVER TRANSPLANTATION

After OLT, to prevent cardiovascular events it is necessary to plan a follow up and a therapy focused on the control of metabolic syndrome manifestations, including control of blood pressure, blood glucose, lipid levels and weight, in addition to encouraging physical activity, and a correct diet. Individualized immunosuppressive therapy should also be designed. Furthermore, it is important to assess the presence of early vascular and cardiac damage, and to recognize their progression by carotid ultrasound and echocardiography, in order to be able to start specific therapy and prevent CV events in the future.

Given the high risk of developing NAFLD after OLT, therapy to prevent its occurrence and/or to treat it, if already developed, should be started. However, currently the only exploitable therapy for NAFLD is diet (Mediterranean diet is recommended<sup>[91]</sup>) and physical activity, although all available data suggest that improving insulin sensitivity could reduce the risk of post OLT NAFLD recurrence or *de novo* development. Drugs as thiazolidinediones (PPAR $\gamma$  agonist with insulin sensitizing effects), metformin, incretin-mimetics (liraglutide), antioxidants (vitamin E), angiotensin converting enzyme inhibitors have given promising results in patients with NAFLD. Several other pharmacological therapies for NAFLD are being studied, such as obeticholic (a syntetic farnesoid X receptor agonist), n-3 polynsaturated fatty acids (PUFA), and novel agents with anti-inflammatory, anti-fibrotic or insulin sensitizing properties [dual PPAR  $\alpha/\delta$  agonists, dual chemokine receptor (CCR)2/CCR5 agonists and fatty acid/bile acid conjugates] and antifibrotic anti-lysyl oxidase-like (anti-LOXL2) monoclonal antibodies<sup>[92]</sup>. While data on pentoxifylline and orlistat have provided limited or inconclusive results, as well as those on lipid lowering drugs (ezetimibe and statins), no clinical trials have been conducted in the post-transplantation setting<sup>[34,76,82,93,94]</sup>.

Thus, at present the only effective approaches for avoiding cardiovascular disease in the post-transplant setting are to prevent and manage MS and its manifestations. Table 3 presents the current available therapies to control metabolic syndrome manifestations.

Also renal dysfunction plays a relevant role in the occurrence of cardiovascular disease and death after transplantation. Therapeutic strategies should be focused to minimize renal injury, particularly in NAFLD patients, for example, by reducing exposure to CNIs<sup>[95]</sup>. This can be accomplished by reducing or withdrawing CNIs after the stable introduction of mycophenolate mofetil, introducing non-CNIs-based immunosuppressive protocols with mTOR inhibitors (sirolimus and everolimus) or reducing the CNIs dose in combination with mTOR inhibitors. The use of such

protocols will require further prospective studies within the context of liver transplantation<sup>[95]</sup>.

### **Problems that remain to be resolved**

The onset of cardiovascular modifications after OLT remains poorly understood, the timing in which these modifications occur after OLT is still being debated. Only a few studies (based on paediatric population and prevalently on kidney transplant) and a meta-analysis<sup>[96-103]</sup> have shown that after solid organ transplantation there was a rapid increase of subclinical atherosclerosis evaluated by aortic stiffness and carotid intima-media thickness.

A recent study<sup>[104]</sup> demonstrated that at 1 year post-transplant, independently of the indication to OLT, LT recipients have similar pro-atherosclerotic profiles as patients with NASH, as measured by endothelial biomarkers and inflammatory cytokines, even when conventional cardiovascular risk factors, such as obesity or elevated Hs-CRP or/and high FRS, are not observed.

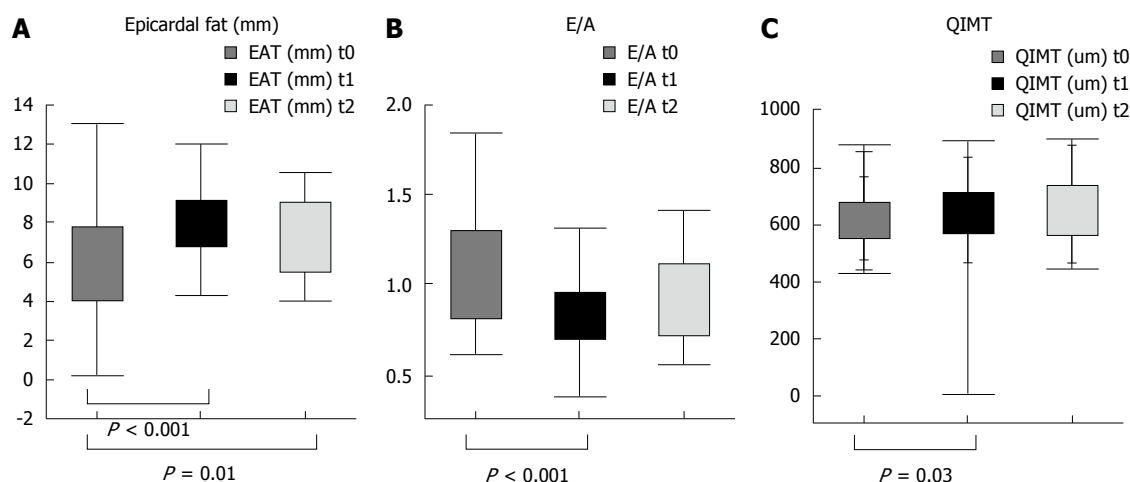
## OUR PRELIMINARY RESULTS

We are conducting a prospective study aimed to understand the types of cardiovascular modifications and their time of development after OLT. Seventy-nine patients in a liver transplant list, were enrolled from 2014 and followed for 2 years after transplant. In these patients cardiovascular, biochemical and anthropometrical parameters were assessed at admission to the transplant waiting list, and at 6, 12, and 18 mo after transplant. The cardiovascular study included: evaluation of cIMT, presence of plaques by carotid ultrasound, diastolic function (E/A), interventricular septum, ventricular mass, and epicardial fat thickness evaluation by echocardiography. Preliminary data showed that cIMT progressively increased during follow up, starting as early as the 6th month, while prevalence of plaques was similar pre and post-transplant. A significant decrease of diastolic function (E/A) and an increase of inter-ventricular septum was observed from enrollment to 6 mo, which then remained stable over time. A progressive increase of epicardial fat was observed during follow up, while ejection function, and ventricular mass did not significantly differ. These preliminary results are shown in Figure 1.

It is yet to be determined if different immunosuppressive therapies influence these early changes and/or if other predisposing factors contribute to cardiac and vascular damage.

### **Future research directions that may maximize practical impact on the field**

OLT candidates and recipients should be carefully evaluated and followed up not only for liver, but also for metabolic complications, optimizing the follow up



**Figure 1** Modification of cardiovascular parameters during follow up: dark grey enrollment, black 6<sup>th</sup> mo, light grey 12<sup>th</sup> mo. A: Epicardial adipose thickness (EAT) significantly increased from baseline to 6<sup>th</sup> mo; B: Diastolic function (E/A) worsened significantly from baseline to 6<sup>th</sup> mo; C: Intima-media thickness (IMT) increased significantly from baseline to 6<sup>th</sup> mo.

**Table 3** Post transplant metabolic syndrome manifestations and their possible therapy

Disease	Suggested therapy	Contraindicated therapy	Ref.
Diabetes mellitus	<p>Insuline: in the early post-operative setting</p> <p>Life-style modification (diet, physical activity)</p> <p>Oral hypoglycemic agent (after steroids tapering):</p> <p>Metformin: less weight gain and hypoglycemia</p> <p>Thiazolidinediones: well tolerated, may improve post-LT NAFLD</p> <p>Dipeptyl peptidase-4 (DPP4) inhibitors, well tolerate, no weight gain, no hypoglycemia, potential anti-inflammation, antihypertension, antiapoptosis effects and immunomodulation on the heart, vessels, and kidney, independent of their hypoglycemic effect</p>	<p>Metformin: not usable with renal failure (lactic acidosis)</p> <p>Thiazolidinediones: may be associated to hepato and cardiotoxicity and are adipogenic</p> <p>Second generation sulfonylureas: determine weight gain, hypoglycaemia, may increase CNI level</p> <p>Meglitinides: determine weight gain, hypoglycemia (only with renal insuff), CNI may increase repaglinide level, are expensive</p> <p>Alpha-glucosidase inhibitors: determine gastrointestinal side effects, are less effective, are expensive</p> <p>Selective renal sodium glucose co-transporter 2 (SGLT 2): dapagliflozin, canagliflozin, empagliflozin, well tolerated but reported hepato-toxicity, contraindicated in patients with renal impairment</p>	[130-133,151-157]
Hyperlipidemia	<p>Hypercholesterolemia responds to:</p> <p>HMGCoA inhibitors (statins): pravastatin is the most studied and used but also atorvastatin, simvastatin, lovastatin, cerivastatin and fluvastatin are used</p> <p>Diet rich in omega 3 fatty acids, fruits, vegetables and dietary fiber</p> <p>Hypertriglyceridemia responds to:</p> <p>Fish oil (omega 3)</p> <p>Fibric acid derivatives (gemfibrosil, clofibrate, fenofibrate)</p>	<p>Statins (except pravastatin and flevastatin) are metabolized by cytochrome P-450 3A4, the same that metabolize CNIs and sirolimus so they must be used with caution because of myotoxicity</p> <p>If used with statins fibrates may increase calcineurin inhibitors levels</p>	[134-138]
Arterial hypertension	<p>First line agents: calcium channels blockers (amlodipine, isradipine, felodipine)</p> <p>Second line agents: specific <math>\beta</math>-blockers, ACE inhibitors, angiotensin receptors blockers and loop diuretics</p>	<p>Nifedipine may increase CNI levels and may cause leg edema</p> <p>ACE inhibitors and angiotensin receptors blockers may exacerbate CNI-induced hyperkalemia, but may provide anti-fibrotic properties and possibly protect against calcineurin induced renal injury</p> <p>Thiazides and other diuretics must be used with close follow-up because of potentiation of electrolyte abnormalities, hyperuricemia and renal dysfunction</p>	[139-141]
Obesity	<p>Bariatric surgery: well tolerated and successful but require a complex reoperation</p> <p>Gastric banding at the time of liver transplant procedure seems successful and well tolerate</p>	<p>Orlistat (tetrahydrolipstatin), inhibitor of pancreatic lipase has limited efficacy and possibly interferes with immunosuppressive therapy</p> <p>Gastric bypass surgery can affect intestinal drug absorption</p>	[141-144]



by introducing blood tests and imaging approaches that are able to show early metabolic, cardiovascular and atherosclerotic alterations.

New parameters that are able to identify subjects at higher metabolic/cardiovascular risk should be identified to plan personalized therapy, including nutritional rules and physical activity.

Prospective studies aimed to evaluate the development of early atherosclerotic damage are needed to understand the timing in which a specific therapy should be started.

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